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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BABIC, CHRISTOPHER M	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/840,208	XIE ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :7/22/2004; 7/26/2004; 9/29/2005.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, claim(s) 1-11, 20, and 21, in the reply filed on November 16, 2006 is acknowledged.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claim(s) 1-5, 10, 11, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al. (U.S. 2003/0054386 A1) in view of Bao et al. (U.S. 6,251,601 B1).

With regard to claim(s) 1, Antonarakis teaches methods of high throughput detection of chromosomal abnormalities ([0011]-[0030]; examples 2-4, for example). Specifically, Antonarkis teaches methods comprising: a) making a polymerase chain reaction (PCR) mixture ([0080]; [0117], for example) by mixing in a vessel components comprising: (i) eukaryotic genomic DNA [0075]; [0116], for example); (ii) a plurality of pairs of forward and reverse DNA primer oligonucleotides wherein one primer of each

said pair is complementary to a 3' sequence of a targeted segment of a first DNA strand of the eukaryotic DNA and the other primer is complementary to the 3' sequence of the second strand of the targeted segment, the length of the segment of eukaryotic DNA being between about 50 and about 300 base pairs ([0053]; [0117], for example), wherein one of the primers of each pair has a detectable label attached to its 5' end ([0079]; i.e. primers with detectable labels; primers necessarily have a free 3'OH and thus, since there is no definition of the term 5'end, any detectable label contained within the primer sequence can be considered attached to the 5'-end), and wherein a plurality of the pairs of primers are each targeted to a segment of a selected different chromosome of interest which is indicative of a potential chromosomal disorder and one pair is targeted for a segment of a control gene which is present on a chromosome other than one on which there is a targeted segment and does not target any chromosome segment that might be indicative of a potential aneuploidy ([0015]-[0028]; [0116], SIM2 and SIM1 on chromosome 21 and 6, respectively, testing for trisomy 21, for example); and iii. PCR buffers and enzymes necessary to carry out PCR amplification; b) conducting a PCR for between about 5 and about 60 temperature cycles to create amplified PCR products ([0117], 35 cycles, for example).

With regard to claim(s) 3 and 4, Antonarakis teaches detection of DiGeorge's and Down's syndrome (table 2, for example).

With regard to claim(s) 5, Antonarakis teaches fluorescent labels ([0079]; for example).

It is noted that Antonarakis teaches the use of paralogous gene sets (table 1, for example) to determine chromosomal abnormalities (fig. 9, for example) so that identical primers can be used to amplify both genes on the separate chromosomes ([0112]-[0113], for example). However, it is first submitted that the claimed invention does not preclude the use of paralogous genes. Furthermore, it is submitted that the concept behind the detection methods of Antonarakis and the instant invention are the same, as demonstrated by the teachings of Antonarakis, which highlight that, "Deviations from a 1:1 ratio of target to reference gene indicates an individual at risk for a chromosomal abnormality ([0085] and [0088], for example).

Due to the sequence homology of the paralogous genes, Antonarakis chooses sequencing methods to determine the copy number based ratio needed to determine if a chromosomal abnormality is present ([0082]-[0086], for example), and thus, does not expressly teach the use of microarrays to detect gene copy numbers as required by steps d-g of claimed invention.

It is further submitted that the use of microarrays for the parallel examination of high numbers of gene sequences was well known in the art at the time of invention. Bao provides a supporting disclosure that teaches methods of detecting chromosomal abnormalities, including that of Down's Syndrome (col. 18, lines 50-55, for example) through the use of microarrays (col. 2-3, for example). Specifically, Bao teaches PCR amplification of sample DNA (col. 12, lines 20-30, for example), subsequent hybridization of single-stranded DNA to microarrays (col. 13, lines 30-60, for example), and array detection with result assessment as it relates to the presence or absence of a

chromosomal disorder (col. 15-18, array detection, for example). As noted above, the use of microarrays for the parallel examination of high numbers of gene sequences was considered standard practice in the art at the time of invention. Bao specifically highlights that array target elements may be replicated several times to provide better results (col. 10, lines 35-50, for example).

With regard to claim(s) 2, Bao teaches application of rule-based algorithms (col. 16, lines 15-35; col. 17, lines 10-20, for example).

With regard to claim(s) 10, Bao teaches probes of about 25 to about 60 nucleotides (col. 8, lines 25-35, for example).

With regard to claim(s) 11, 20, and 21, Bao teaches comparing microarray results to correct for background, i.e. normalization of array results (col. 17-18, for example). Specifically, Bao teaches determination of an "I-ratio" (col. 18, lines 10-45, B/D, genomic test, for example), "N-ratio" (Bg/Dg, genomic DNA "normal" subgroup, for example), and a "C-fatctor" (normalized B/D ratio, for example). With regard to gender specific averages, Bao teaches the use of microarrays for genomic disease managment, including diseases that are more likely to occur in one gender (e.g. breast cancer, females, for example). Thus, it would have been *prima facie obvious* to obtain averages from a specific gender.

In summary, it is submitted that it would have been *prima facie obvious* to a practitioner of ordinary skill in the art at the time of invention to incorporate the microarray detection methods to the amplicons of Antonarakis to detect chromosomal disorders since well known scientific methodology as demonstrated by Bao suggests

such a modification to provide for parallel examination of high numbers of gene sequences, thus arriving at the claimed invention.

2. Claim(s) 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al. (U.S. 2003/0054386 A1) in view of Bao et al. (U.S. 6,251,601 B1) as applied claim(s) 1-5, 10, 11, 20, and 21 above, and in further view of Fulcrand et al. (U.S. 6,319,674 B1).

With regard to claim(s) 6-8, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach primer pairs, one having a phosphate group as well as one having a fluorescent group, and subsequent digestion of the phosphate labeled primer with an exonuclease.

Fulcrand provides a supporting disclosure that teaches methods of generating labeled single stranded DNA utilizing phosphate labeled primers (col. 26, lines 10-35, for example). Specifically, Fulcrand, teaches primer pairs, one having a phosphate (col. 26, lines 15-20, for example) group as well as one having a fluorescent group (col. 26, lines 15-20, Cy3, for example), and subsequent digestion of the phosphate labeled primer with an exonuclease (col. 26, lines 20-25, lamda exonuclease, for example).

In summary, it is submitted that it would have been *prima facie obvious* to a practitioner of ordinary skill in the art at the time of invention to incorporate primer pairs, one having a phosphate group as well as one having a fluorescent group, and

subsequent digestion of the phosphate labeled primer with an exonuclease within the methods suggested by Antonarakis and Bao since Fulcrand suggests such a modification to produce labeled single stranded DNA for subsequent hybridization to microarrays, thus arriving at the claimed invention.

3. Claim(s) 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al. (U.S. 2003/0054386 A1) in view of Bao et al. (U.S. 6,251,601 B1) as applied claim(s) 1-5, 10, 11, 20, and 21 above, and in further view of Lockhart et al. (U.S. 6,040,138).

With regard to claim(s) 9, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach GAPD as a control gene.

Lockhart provides a supportive disclosure that highlights GAPD as a common "housekeeping" gene used as a expression level control on microarrays (col. 16, lines 30-65, for example). Thus, Lockhart demonstrates that GAPD was well known in the art to be an excellent control gene capable or providing a reliable base line for array detection procedures.

As noted above, Antonarakis teaches the use of paralogous gene sets (table 1, for example) to determine chromosomal abnormalities (fig. 9, for example) so that identical primers can be used to amplify both genes on the separate chromosomes ([0112]-[0113], for example). However, it is first submitted that the claimed invention

does not preclude the use of paralogous genes. Furthermore, it is submitted that the concept behind the detection methods of Antonarakis and the instant invention are the same, as demonstrated by the teachings of Antonarakis, which highlight that, "Deviations from a 1:1 ratio of target to reference gene indicates an individual at risk for a chromosomal abnormality ([0085] and [0088], for example).

Furthermore, Antonarakis expressly teaches identification of such paralogous genes ([0060]-[0073], for example).

In summary, it is submitted that it would have been *prima facie obvious* to a practitioner of ordinary skill in the art at the time of invention to simply amplify the targeted gene of interest and a well known control gene within the methods of Antonarakis instead of paralogous genes to circumvent the time needed to identify such paralogous genes.

Conclusion

Claim(s) 1-11, 20, and 21 are rejected. No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Holzgreve et al. (EP 1 329 517 A1). Holzgreve teaches the detection of chromosomal abnormalities, such as trisomy 21, through multiplex RT-PCR, instead of genomic DNA copy number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M. Babic
Patent Examiner
AU 1637

4/23/07

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

4/30/07